# Assessment of cardiovascular function by combining clinical data with a computational model of the cardiovascular system

Koichi Sughimoto, MD, PhD,[a] Fuyou Liang, PhD,[b,c] Yoshiharu Takahara, MD, PhD,[d] Kenji Mogi, MD, PhD,[d] Kenji Yamazaki, MD, PhD,[a] Shu Takagi, PhD,[b] and Hao Liu, PhD[c,e]

**Objective:** A sufficient understanding of patients' cardiovascular status is necessary for doctors to make the best decisions with regard to the treatment of cardiovascular disease; however, it is often not available because of the limitation of clinical measurements. The objective of this study was to examine whether cardiovascular function can be assessed quantitatively and for specific patients by combining clinical data with a computational model of the cardiovascular system.

**Methods:** Seven consecutive patients undergoing off-pump coronary artery bypass grafting were enrolled in this study. The clinical data were collected both during the preoperative diagnosis and during the operation. Sensitivity analysis was performed to select the major model parameters most relevant to the measured data. The major model parameters were then estimated through a data-fitting procedure, enabling a patient-specific quantitative assessment of various aspects of cardiovascular function.

**Results:** The results revealed the prevalence of left ventricular diastolic dysfunction in the patients, although the severity of dysfunction exhibits significant interpatient variability (the estimated left ventricular passive elastance varies from 194% to 540% of its reference value). Moreover, 4 of the 7 patients studied had impaired left ventricular systolic function.

**Conclusions:** The current study demonstrates the feasibility of assessing cardiovascular function quantitatively by combining clinical data with a cardiovascular model. In particular, the assessment utilizes the measurements already in use or available in clinical settings, enhancing the clinical potential of the proposed method. (J Thorac Cardiovasc Surg 2013;145:1367-72)

A good understanding about the cardiovascular status of a patient is necessary for clinical staff members to make proper decisions.[1] This is particularly relevant to patient management in the intensive care unit (ICU), where stabilizing patients' hemodynamic state is a crucial issue.[2] The Swan-Ganz catheter (Edwards Lifesciences, Irvine, Calif) is one of the most important pieces of equipment used in the ICU, providing real-time monitoring of many important cardiovascular variables (eg, central venous pressure, pulmonary arterial pressure, and cardiac output).[3] The measured data are, however, usually not a direct indicator of cardiovascular function, such as systolic contractility and diastolic relaxation of the left ventricle. As a consequence, bedside hemodynamic management currently remains highly dependent on the experience of the attending clinical staff. This pitfall may lead to a suboptimal outcome or prolonged hospitalization.

A well-known advantage of a computational model is that it can account for the combined effects on hemodynamics of various cardiovascular properties.[4,5] This naturally raises an issue regarding whether some cardiovascular properties may be derived provided that some hemodynamic variables are known, such as those measured in clinical practice. This issue has stimulated a variety of studies, including those carried out within a purely theoretical framework,[6] those based on animal in vivo experiments,[7-10] and those based on mock circulatory system experiments,[11] among others. These studies suggest that clinical-data-based modeling of the cardiovascular system has the potential for assisting doctors in acquiring a better understanding of a patient's condition. In particular, recent studies[7-10] demonstrated that some aspects of cardiac function can be assessed reasonably by incorporating a limited number of data available in the clinical setting into a cardiovascular model—a remarkable

From the Department of Cardiovascular Surgery,[a] The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo, Japan; the Organ and Body Scale Team,[b] Computational Science Research Program, The Institute of Physical and Chemical Research, Wako, Saitma, Japan; Shanghai Jiao Tong University and Chiba University International Cooperative Research Centre (SJTU-CU ICRC),[c] Shanghai Jiao Tong University, Shanghai, China; Division of Cardiovascular Surgery,[d] Funabashi Municipal Medical Center, Chiba, Japan; and Graduate School of Engineering,[e] Chiba University, Chiba, Japan.

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Address for reprints: Koichi Sughimoto, MD, PhD, Department of Cardiovascular Surgery, The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo, Japan, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan (E-mail: ksughimoto@gmail.com); or Fuyou Liang, PhD, the Organ and Body Scale Team, Computational Science Research Program, The Institute of Physical and Chemical Research, Wako, Japan, 2-1 Hirosawa, Wako, Saitama, 351-0198, Japan (E-mail: fyliang@riken.jp).

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**Abbreviations and Acronyms**

$C_{svn}$ = systemic venous compliance
$E_{lva}$ = left ventricular active elastance
$E_{lvp}$ = left ventricular passive elastance
ICU = intensive care unit
LV = left ventricular

step in this field. These previous studies are of great significance in the sense that they pioneered the direction and established a methodological basis; however, the clinical implications of the studies are limited as a result of the absence of patient data-based validation.

The current study, therefore, was carried out with the aim of examining the feasibility of assessing cardiovascular function by incorporating data available in the clinical setting into a computational model of the cardiovascular system. To this end, clinical data were collected from patients who underwent cardiac surgery. A well-posed parameter estimation problem was devised through data selection, sensitivity analysis of model parameters, and use of suitable parameter estimation algorithms. The obtained results were investigated in relation to the clinical symptoms of the patients.

## MATERIALS AND METHODS

### Patients and Data Collection

Seven consecutive patients who underwent off-pump coronary artery bypass graft surgery were enrolled in the current study. The clinical diagnosis for these patients revealed angina pectoris in 5 patients, old myocardial infarction in 1 patient, and coexisting angina pectoris and old myocardial infarction in 1 patient. All the patients were free of severe cardiac valvular lesions. At least 3 anastomoses were created for each patient. The left intrathoracic artery was used to bypass an left anterior descending artery lesion. When necessary, the right intrathoracic artery, the radial artery, and the saphenous veins were used. During the surgery, the patients were subjected to usual anesthesia with fentanyl and sevoflurane without the implementation of cardiopulmonary bypass or intra-aortic balloon pump. The study was reviewed and approved by the ethics committee of RIKEN. Written consent was received from all patients.

Data collection was conducted both during the preoperative diagnosis and during surgery. The preoperative data consist of patients' demographics (such as age, sex, weight, height) and the echocardiography data on the left ventricle. The perioperative data include central venous pressure, pulmonary arterial pressure, heart rate and cardiac output (measured using a Swan-Ganz catheter), and blood pressure in the radial artery. These data were recorded as a temporal sequence data by a Vigilance monitor (Edwards Lifesciences) and were stored in a computer connected to the monitor. Data recording started from the administration of anesthesia and lasted until the next day when the patient was extubated with stabilized hemodynamic status. A summary of the patient characteristics and measured data is given in Table 1.

### Cardiovascular Model

A simple cardiovascular model with a limited number of parameters would be preferred in consideration of the purpose of the current study. On the other hand, the model should carry sufficient details to account for the major characteristics of blood circulation, such as cardiac dynamics and its interaction with pre- and posthydraulic load. According to these guidelines, compartmentalization of the cardiovascular system was implemented first, yielding 3 series-arranged compartments that represent the heart, the systemic circulation, and the pulmonary circulation. Each compartment was then represented by a specific combination of lumped parameters that account for the hemodynamic changes induced by the compartmentalization. The governing equations for blood flow were formulated by imposing mass conservation and momentum conservation over the system. The pumping characteristics of each of the 4 cardiac chambers (ie, right atrium, right ventricle, left atrium, left ventricle) were represented by a specific time-varying elastance curve.[12] The resulting equation system was solved using a fourth-order Runge-Kutta method. Similar models have been used in our previous studies,[5,13] which provide more details on model development, governing equations, and numeric methods.

### Estimation of Model Parameters Based on Clinical Data

To reduce the complexity of the parameter estimation system, we restricted the number of clinical data involved by selecting the data that characterize most dominantly the status of blood circulation as the input (herein called "primary data") into the system. The selected primary data included mean central venous pressure, mean pulmonary arterial pressure, mean systemic arterial pressure, cardiac output, and left ventricular (LV) end-systolic volume index. The cardiovascular model contains many more parameters ($n = 45$), and hence a unique solution is not obtainable if all model parameters are involved in the parameter estimation problem. To tackle this problem, sensitivity analysis was performed on the model to identify the parameters (herein called "major model parameters") that dominate the model-predicted counterpart of the selected primary data. As a consequence, the 5 most dominant model parameters were identified and designated as the major parameters and include systemic peripheral resistance, systemic venous compliance ($C_{svn}$), right ventricular active elastance, LV passive elastance ($E_{lvp}$), and LV active elastance ($E_{lva}$). In terms of the definition of cardiac elastances in the current model, passive elastance represents the baseline ventricular chamber stiffness in diastole and hence is an important indicator of ventricular diastolic function.[5,12-14] Active elastance represents the maximum increase in chamber stiffness induced by myocardial contraction during systole and hence is a measure of ventricular systolic function.[5,12]

Subsequently, the values of the major model parameters were adjusted with the Nelder-Mead method[15] that operates to minimize the $L_2$ error between model predictions and measurements. Herein, convergence is justified when the error is reduced to < 0.1%. This process is called model patient specification because it results in a set of estimated model parameters that characterize the cardiovascular function of a specific patient. It should be noted that the secondary model parameters (parameters apart from the major ones) were held constant at their default values during parameter estimation.

## RESULTS

Model parameter estimation was performed for each patient using the preoperative LV echocardiographic data combined with the data acquired at a time point during the operation (after anesthesia induction and before the implementation of the coronary artery bypass graft surgery when patient hemodynamics are in a relatively stable state).

### Results of Model Parameter Estimation

The predicted cardiovascular variables are compared with their measured counterparts in Table 2, with the estimated model parameters reported in Table 3. In Table 3, the parameters are normalized relative to their reference

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**TABLE 1. Patient characteristics**

| Patient no. | Gender | Age, y | Diagnosis | BW, kg | Ht, cm | LVEDVI, mL/m$^2$ | LVESVI, mL/m$^2$ | LVEF, % |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 70 | AP | 74 | 161 | 35.5 | 12.4 | 65 |
| 2 | M | 70 | AP | 62 | 161 | 58.8 | 33.9 | 42.3 |
| 3 | M | 78 | AP | 68 | 162 | 44.4 | 13.3 | 70 |
| 4 | M | 70 | OMI | 57 | 164 | 91.6 | 48.6 | 47 |
| 5 | M | 64 | AP | 53.5 | 154 | 50.4 | 19.2 | 62 |
| 6 | M | 62 | AP | 66 | 169 | 61.3 | 24.6 | 51 |
| 7 | F | 55 | AF, OMI | 78 | 172 | 61 | 21.2 | 65 |

*BW*, Body weight; *Ht*, height; *LVEDVI*, left ventricular end-diastolic volume index; *LVESVI*, left ventricular end-systolic volume index; *LVEF*, left ventricular ejection fraction; *M*, male; *AP*, angina pectoralis; *OMI*, old myocardial infarction; *F*, female; *AF*, atrial fibrillation.

values. The reference parameter values characterize the normal cardiovascular function of adult subjects.[4,5,16]

A quadrant illustration of LV function is given in Figure 1, in which each patient is distributed in 1 of 4 quadrants based on the estimated normalized $E_{lva}$ and normalized $E_{lvp}$. The 7 patients are distributed in 3 quadrants—3 in quadrant I, 1 in quadrant III, and 3 in quadrant IV. Quantitatively, the estimated normalized $E_{lvp}$ for 6 patients was > 1 (range, 1.9-5.4), indicating increased chamber stiffness of the left ventricle in diastole. Moreover, the estimated normalized $E_{lva}$ for 4 patients was < 1 (range, 0.32-0.85), indicating impaired systolic function.

It should be noted that because of the absence of patient-specific data on total blood volume, all patients were assigned the same total blood volume in the model and $C_{svn}$ was modified to adjust the preload of the right heart. In this sense, estimated $C_{svn}$ has limited physiologic significance and thus is not discussed in the sections that follow.

### Left Ventricular Pressure–Volume Curve

With the major model parameters estimated, the LV pressure–volume curve was derived for all patients from the computations. The pressure–volume curves clearly show the different cardiovascular functional characteristics of the 7 patients (Figure 2).

## DISCUSSION

### Characteristics of Assessed Cardiac Function

Most patients studied were found to have LV diastolic dysfunction, and 3 patients had combined LV diastolic dysfunction and systolic function impairment. The results are consistent with the general physiologic features of patients with coronary artery disease,[17,18] confirming, in

**TABLE 2. Comparison of measured and predicted cardiovascular variables**

| Patient no. | $P_{vm}$, mm Hg | $P_{pm}$, mm Hg | $P_{am}$, mm Hg | LVESVI, mL/m$^2$ | SVI, mL/m$^2$ | $L_2$ Error, %* |
|---|---|---|---|---|---|---|
| 1 | | | | | | |
| Meas. | 8.5 | 19 | 67 | 12.4 | 23.1 | 0.07 |
| Pred. | 8.5 | 19 | 67 | 12.4 | 23 | |
| 2 | | | | | | |
| Meas. | 13.5 | 21 | 65 | 33.9 | 24.9 | 0.07 |
| Pred. | 13.5 | 21 | 65 | 33.8 | 24.9 | |
| 3 | | | | | | |
| Meas. | 6.5 | 14 | 73 | 13.3 | 31.1 | 0.04 |
| Pred. | 6.5 | 14 | 73 | 13.3 | 31.1 | |
| 4 | | | | | | |
| Meas. | 5.5 | 11 | 48 | 48.6 | 43 | 0.07 |
| Pred. | 5.5 | 11 | 48 | 48.6 | 43 | |
| 5 | | | | | | |
| Meas. | 10.5 | 20 | 77 | 19.2 | 31.2 | 0.09 |
| Pred. | 10.5 | 20 | 77 | 19.2 | 31.3 | |
| 6 | | | | | | |
| Meas. | 8.5 | 17 | 80 | 24.6 | 36.7 | 0.05 |
| Pred. | 8.5 | 17 | 79.9 | 24.6 | 36.7 | |
| 7 | | | | | | |
| Meas. | 6.5 | 21 | 79 | 21.2 | 39.8 | 0.06 |
| Pred. | 6.5 | 21 | 79 | 21.2 | 39.8 | |

$P_{vm}$, Mean central venous pressure; $P_{pm}$, mean pulmonary arterial pressure; $P_{am}$, mean systemic arterial pressure; *LVESVI*, left ventricular end-systolic volume index; *SVI*, systolic volume index; *Meas.*, measured; *Pred.*, predicted. *The root mean square of the errors among the 5 primary measurements and the corresponding predictions.

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part, the validity of the proposed method. On the other hand, the results show high interpatient variability in terms of the severity of diastolic/systolic dysfunction. According to the estimated LV passive/active elastances, each patient can be located uniquely in a 4-quadrant graph in which each quadrant represents a specific functional state of the left ventricle. Herein, quadrant I represents normal systolic function but degenerated diastolic function, quadrant II represents an optimal ventricular functional state featured by normal systolic function and normal diastolic function, quadrant III represents normal diastolic function but impaired systolic function, and quadrant IV represents the worst condition in which both systolic and the diastolic functions are abnormal. As seen in Figure 1, none of our patients was at an optimal ventricular functional state.

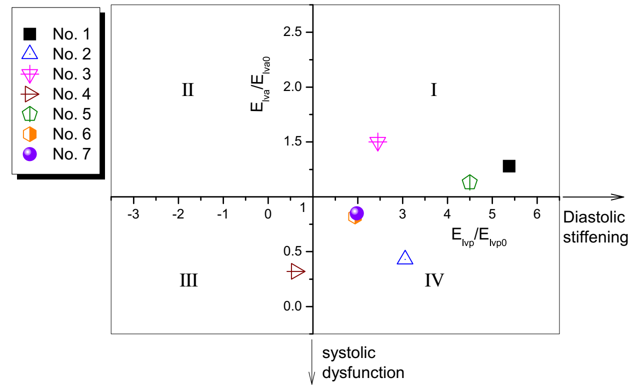


**FIGURE 1.** Distribution of the patients according to the estimated $E_{lva}/E_{lva0}$ and $E_{lvp}/E_{lvp0}$. The point where $E_{lva}/E_{lva0} = 1$ is set to be the normal point. The patients with $E_{lva}/E_{lva0} < 1$ are classified as having systolic dysfunction whereas those with $E_{lvp}/E_{lvp0} > 1$ are classified as having diastolic dysfunction. Quadrant I: normal systolic function and degenerated diastolic function, quadrant II: an optimal ventricular functional state, quadrant III: normal diastolic function and impaired systolic function, and quadrant IV: both systolic and the diastolic functions are abnormal. $E_{lva}/E_{lva0}$, Normalized left ventricular active elastance; $E_{lvp}/E_{lvp0}$, normalized left ventricular passive elastance.

## Clinical Implications

It has been demonstrated that ventricular function is an important determinant of the hemodynamic response to alterations in cardiac preload/afterload.[14,19] For instance, diastolic stiffening of the left ventricle increases the dependence of cardiac output on ventricular preload and diminishes the cardiac output response to enhancement in ventricular contractility,[20] whereas ventricular systolic stiffening increases the lability of LV (arterial) systolic pressure with LV preload alteration.[21] Therefore, a treatment may result in different outcomes, depending on the cardiovascular functional status of the patient. The viewpoint is supported by a recent clinical study in which patients with heart failure and preserved ejection fraction were found to experience greater blood pressure reduction, less enhancement in cardiac output, and a greater likelihood of stroke volume drop with vasodilators when compared with patients with heart failure and reduced ejection fraction.[22] The issue is especially important for patient management in the ICU, because critically ill patients are usually highly variable in their response to care and treatment.[1,10] Therefore, the more sufficient our understanding of the cardiovascular function of a patient, the more likely that proper ICU care is provided.

Clinical data available in the ICU, such as electrocardiograms, blood pressures, ventricular volume, cardiac output, and so forth, carry plenty of information related to cardiovascular function; they do not, however, indicate cardiovascular function directly because of the complex interrelationships among them. Our proposed method offers a practical means to transform discrete clinical data into a physiologic picture from which many aspects of cardiovascular function are known directly. The information obtained may help clinical staff members refine the diagnosis and improve patient management. For example, for patients with isolated LV systolic dysfunction, administrating catecholamines would increase cardiac output by enhancing LV contractility, whereas for patients with diastolic dysfunction, reducing afterload by administrating vasodilators (such as milrinone [phosphodiesterase-3 inhibitor]) would be a more effective means to preserve cardiac output than enhancing cardiac contractility by administrating

**TABLE 3. Estimated model parameters**

| Patient no. | $C_{svn}/C_{svn0}$ | $E_{lvp}/E_{lvp0}$ | $E_{lva}/E_{lva0}$ | $R_s/R_{s0}$ | $E_{rva}/E_{rva0}$ |
|---|---|---|---|---|---|
| 1 | 0.68 | 5.38 | 1.28 | 1.07 | 0.5 |
| 2 | 0.28 | 3.06 | 0.43 | 0.94 | 0.33 |
| 3 | 1.18 | 2.45 | 1.5 | 0.95 | 0.82 |
| 4 | 1.51 | 0.62 | 0.32 | 0.58 | 3.91 |
| 5 | 0.45 | 4.5 | 1.13 | 1.27 | 0.44 |
| 6 | 0.72 | 1.94 | 0.82 | 0.84 | 0.79 |
| 7 | 0.72 | 1.98 | 0.85 | 0.61 | 4.38 |

Reference values of the parameters: $C_{svn0} = 85.7$ mL/mm Hg, $E_{lvp0} = 0.058$ mm Hg/mL, $E_{lva0} = 2.49$ mm Hg/mL, $R_{s0} = 1.1$ mm Hg/s per milliliter, $E_{rva0} = 0.43$ mm Hg/mL. Accuracy of estimation: Further reducing the errors (the $L_2$ errors given in Table 2) between measurements and predictions leads to less than ± 1% changes in the estimated model parameters relative to the values given in the table. $C_{svn}/C_{svn0}$, Normalized systemic venous compliance; $E_{lvp}/E_{lvp0}$, normalized left ventricular passive elastance; $E_{lva}/E_{lva0}$, normalized left ventricular active elastance; $R_s/R_{s0}$, normalized systemic resistance; $E_{rva}/E_{rva0}$, normalized right ventricular active elastance.

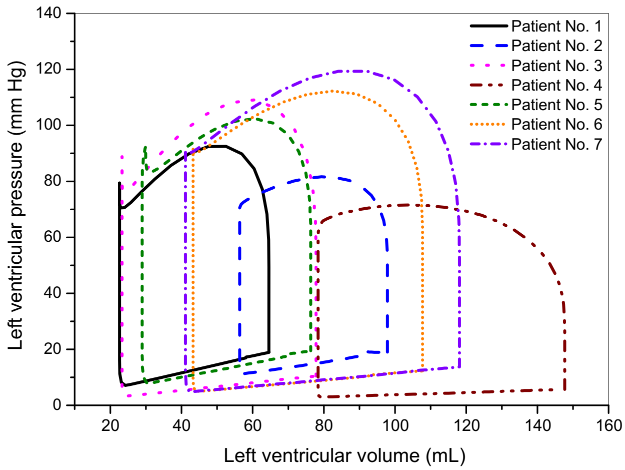


**FIGURE 2.** Model-predicted left ventricular pressure–volume loops for the patients studied.

catecholamines. That is to say, with a clear understanding of cardiovascular function, doctors may implement hemodynamic management more effectively and safely by choosing the right interventions and administrating the correct medicines at the correct dose. The clinical applicability of the proposed method is also supported by the fact that it does not require any instrumentation beyond what is already in use or available in clinical settings, and it demands little computer resources (the computation can be completed within minutes on a personal computer).

### Methodological Significance

Estimation of cardiovascular function from measured hemodynamic data has been addressed extensively in the literature.[6-11] The majority of existing studies is based on animal experiments,[7-10] with the remainder conducted either within a purely theoretical framework[6] or based on mock circulatory system experiments.[11] The current study is, to the best of our knowledge, the first attempt to address the issue with the clinical data of patients in ICU. Moreover, although various parameter-estimating schemes have been proposed in previous studies, such as the linear proportional gain-based method[7-10] and the solution library-based interpolation method,[6] we used a modified Nelder-Mead method in consideration of the clinical data available in the current study, and we proved it to be fast and robust for the current problem.

### Limitations

The major limitation of the current study is associated with the insufficiency of clinical data. For example, the absence of data on blood pressure in the left atrium or the pulmonary veins prevents the estimate of the pulmonary resistance and reduces the accuracy of the assessed LV diastolic function. The lack of right ventricular volume data hampers an accurate estimate of the systolic/diastolic function of the right ventricle. In addition, echocardiographic measurement of the left ventricle was performed during preoperative diagnosis, which implies the presence of a potential mismatch between the LV volumetric data and the data measured during operation. Although we have selected the perioperative data taken at the moment when catheter-measured ventricular stroke volume matches the LV echocardiographic data, the time-varying nature of patients' physiologic conditions determines that the data mismatch cannot be avoided completely. Fortunately, the aforementioned limitations may be overcome with the aid of available clinical measurement techniques. Left atrial (or pulmonary venous) pressure can be determined indirectly by measuring pulmonary wedge pressure using a Swan-Ganz catheter with an inflatable balloon.[23,24] LV volume can be measured during the operation with transesophageal echocardiography.[25] In particular, with the limitations overcome, the proposed method could be applied to assess cardiovascular function during the entire operation rather than at a specific time point. Another limitation of the current study is associated with the small number of patients involved. In an ongoing study, we have recruited > 30 patients and hope to report our results in the near future.

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